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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,253	06/02/2006	Helen Francis-Lang	05-967-A5	4136

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,253	FRANCIS-LANG ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2010 and 19 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,10 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,10 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on August 16, 2010 and November 19, 2010.

Currently, claims 1, 9-10, and 26-29 are pending and under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites "a second" assay system in line 2. The recitation of a "second" assay system necessarily requires a recitation of a "first" assay system. However, neither claim 1 nor claim 29 recites a "first" assay system. In addition, it is unclear how the method steps (d)-(g) should be considered as a "second" assay system. Note that the method steps in claim 1 inherently require the presence of cells expressing UP, otherwise, performing the method step (c) would be impossible. For example, see claim 27, which explicitly recites that the assay system of claim 1 comprises cells expressing UP. Hence, there is no distinguishable difference between the assay system of claim 1and the "second" assay system of claim 29. Accordingly, one of ordinary skill in the art would not be able to ascertain whether the method steps recited in claim 29 are intended to be different from those recited in claim 1, or whether the method steps recited in claim 29 are a mere repetition of those recited in claim 1, thus requiring one to perform two rounds of the same method steps. Therefore, it is concluded that the "additional" method steps recited in claim 29 fail to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 9, 26-27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pizzorno et al. (WO 01/60985 A2, applicant's citation).

Pizzorno et al. teach that uridine phosphorylase (UPase) activity and expression levels are upregulated in human tumors compared to normal tissue. They teach that one can detect and evaluate the presence of malignant tumor cells by detecting UPase activity in a biological sample. They teach that a uridine phosphorylase inhibitor can be used to treat cancer. See pages 3, 83; claims 33, 47; Figure 1. They teach that one can make and use "compositions useful for inhibition of expression of wild type and/or mutant UPase" such that "antisense nucleic acids serve to inhibit the expression, function, or both of wild type UPase and/or mutant UPase". See page 44. They teach that the compositions include "antisense molecules, ribozymes, or double-stranded RNA". See page 45.

Although Pizzorno et al. do not expressly teach that the method of identifying antisense nucleic acids or RNAi-inducing dsRNA "to inhibit the expression, function, or both of wild type UPase and/or mutant UPase" is equivalent to a method of identifying antisense nucleic acids or RNAi-inducing dsRNA to inhibit beta-catenin pathway, it logically follows that the method of Pizzorno et al. would necessarily identify a beta-catenin pathway inhibitor since the method steps of Pizzorno et al. necessarily and inherently comprise all the method steps recited in the rejected claims. Note that in order to identify antisense nucleic acids or RNAi-inducing dsRNA that inhibit the expression of UPase as taught by Pizzorno et al., one must use human tumor cells that are taught to have upregulated UPase expression levels as opposed to normal tissue cells that do not overexpress UPase. In addition, in order to identify antisense nucleic acids or RNAi-inducing dsRNA that inhibit the expression of UPase as taught by Pizzorno et al., one must contact the UPase-overexpressing human tumor cells with the test antisense nucleic acids or RNAi-inducing dsRNA (e.g., "by transfection of cells with antisense molecules." or "antisense molecules of the invention may be made synthetically and then provided to the cell." See page 45) and detect the

inhibited expression levels of UPase in a controlled experiment comprising a control (e.g., no test agent) and an experimental (e.g., test agent). See Figure 2 of Pizzorno et al. demonstrating that it is routine to design experiments comprising "control" having no test agent and experimental groups having the test agent. Further, note that the state of the art pertaining to identifying target expression-inhibiting antisense molecules was sufficiently developed at the time of filing. See page 45 of Pizzorno et al.: "With regard to using antisense molecules to inhibit gene expression, such use is well known in the art." Further, it is obvious and within the technical grasp of one of ordinary skill in the art to repeat the identification method steps (e.g., contacting tumor cells with antisense molecules and detecting reduction of UPase expression levels in comparison with a control group) for verification purpose. Since Pizzorno et al. expressly and implicitly taught and suggested all the method steps claimed in claims 1, 9, 26-27, and 29, one performing the method of Pizzorno et al. would necessarily identify a beta-catenin pathway inhibitory agent, and therefore, the claims taken as a whole would have been *prima facie* obvious at the time of filing.

Claims 1, 9-10, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verma et al. (*Clinical Cancer Research,* 2003, 9:1291-1300, citation of record) in view of Miyashita et al. (*Cancer,* 2002, 94:2959-2966), Deneen et al. (*Molecular and Cellular Biology,* 2003, 23:3897-3908), Pizzorno et al. (WO 01/60985 A2, applicant's citation), Deneen et al. (*Cancer Research,* 2003, 63:4268-4274, citation of record), and Monga et al. (*Gastroenterology,* 2003, 124:202-216, citation of record).

Verma et al. teach that one can use cells that overexpress beta-catenin in order to identify an inhibitor of the beta-catenin signaling pathway, wherein the cells that overexpress beta-

catenin are cancer cells such as HCT116 obtainable from ATCC. They show that an siRNA targeted to beta-catenin reduce tumor cell proliferation as well as beta-catenin expression in HCT116 cells compared to a control (mock) treatment. They show that the treatment of HCT116 with the siRNA targeted to beta-catenin also reduces the expression levels of beta-catenin-dependent genes such as c-myc and cyclin D1. See the entire reference. Verma et al. do not teach using an siRNA/PMO targeted to uridine phosphorylase to identify a beta-catenin pathway inhibitory agent.

Miyashita et al. teach that uridine phosphorylase is highly expressed in the majority (about 77.8%) of tumor cells of oral squamous cell carcinoma and that its expression level is correlated with poor prognosis. They teach that the activity of uridine phosphorylase "appears to be elevated in the tumor tissues compared with the adjacent normal tissues." See page 2965. They teach that amplification of the protooncogene cyclin D1 has been associated with poor prognosis of oral squamous cell carcinoma. See the entire reference.

Deneen et al. (*Molecular and Cellular Biology*) teach cyclin D1 and uridine phosphorylase are upregulated by EWS/ETS fusion proteins (EWS/FLI1, EWS/ERG, and EWS/ETV1) in NIH3T3 cells. See Table 1. They suggest that cyclin D1 and uridine phosphorylase are EWS/ETS target genes playing a role in EWS/ETS-mediated oncogenesis/tumorigenesis.

Deneen et al. (*Cancer Research*) teach that their team as well as others observed that uridine phosphorylase is upregulated and overexpressed in a number of human tumor cells. See page 4268: "In this work, we demonstrate that the metabolic regulator uridine phosphorylase is a biologically relevant EWS/ETS target gene…Uridine phosphorylase had previously been shown to be increased in numerous murine and human tumors and tumor cell lines and is up-regulated

by activation of RAS. We now show that ectopic expression of uridine phosphorylase alone is sufficient to promote anchorage-independent growth of NIH-3T3 cells." They suggest that "uridine phosphorylase contributes to pathways that initiate cellular proliferation" and that "uridine phosphorylase is promoting cellular transformation by impacting other physiological mechanisms directly linked to cellular proliferation or survival". See page 4273, right column.

Pizzorno et al. teach that uridine phosphorylase (UPase) activity and expression levels are upregulated in human tumors compared to normal tissue. They teach that one can detect and evaluate the presence of malignant tumor cells by detecting UPase activity in a biological sample. They teach that a uridine phosphorylase inhibitor can be used to treat cancer. See pages 3, 83; claims 33, 47; Figure 1. They teach that one can make and use "compositions useful for inhibition of expression of wild type and/or mutant UPase" such that "antisense nucleic acids serve to inhibit the expression, function, or both of wild type UPase and/or mutant UPase". See page 44. They teach that the compositions include "antisense molecules, ribozymes, or double-stranded RNA". See page 45.

Monga et al. teach that one can use a PMO antisense molecule to identify a beta-catenin signaling pathway inhibitor, which also functions as a cell proliferation inhibitor, wherein the identification process involves a comparison between PMO antisense-treated cells and negative control antisense-treated cells. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an siRNA or a PMO antisense targeted to the nucleic acid encoding uridine phosphorylase and treat tumor cells with the siRNA/PMO to identify whether the siRNA/PMO inhibits uridine phosphorylase expression in the tumor cells, wherein such identification also identifies an inhibitor of the beta-catenin signaling pathway involving cyclin D1.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success, because an inhibitor (such as an antisense molecule) of uridine phosphorylase was suggested to be useful as an anti-cancer agent as explicitly taught and suggested by Pizzorno et al. and thus identifying a nucleic acid-based uridine phosphorylase inhibitor was an art-recognized goal at the time the invention was made, and because there was a reasonable suggestion that an inhibitor of uridine phosphorylase would reasonably inhibit the protooncogenic/proliferative beta-catenin signaling pathway as suggested by the cited prior art references. For example, it was known in the art that cyclin D1, which is often co-upregulated and overexpressed in conjunction with uridine phosphorylase in tumor cells or proliferating cells, was suggested to be a beta-catenin-dependent gene as an experimental demonstration showing that an siRNA targeted to beta-catenin reduces the expression of cyclin D1 in cancer cells. See Figure 3E of Verma et al. In addition, both uridine phosphorylase and beta-catenin were known to be overexpressed and activated in both lung tumor cells and liver tumor cells. See Figure 2 of Pizzorno et al., Monga et al., and Verma et al. Further, it was art-accepted knowledge that uridine phosphorylase is overexpressed in various human tumor cells and proliferating cells and thus its overexpression was suggested to be a contributing factor for tumor growth/proliferation, (e.g., Pizzorno et al. teach that uridine phosphorylase (UPase) activity and expression levels are upregulated in human tumors compared to normal tissue, thus suggest that an inhibitor of UPase is useful as an anti-cancer agent; Deneen et al. (*Cancer Research*) suggest that "uridine phosphorylase contributes to pathways that initiate cellular proliferation"), and the activation of beta-catenin signaling pathway was known to contribute to tumor cell proliferation as taught by Monga et al. and Verma et al. Hence, based on the overlapping expression/activity levels and functional roles between uridine phosphorylase, cyclin D1, and beta-catenin in tumor

cells/proliferating cells, one of ordinary skill in the art would have reasonably predicted that an inhibitor of uridine phosphorylase is likely to also inhibit beta-catenin signaling, and further, it would have been obvious to one of ordinary skill in the art to use tumor cells (e.g., liver tumor cells or colon tumor cells) that not only overexpress UPase and but also have activated beta-catenin signaling pathway so as to identify a PMO or an siRNA molecule that inhibits not only tumor cell growth but also the expression levels of UPase. Accordingly, the claims taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita (AU1637, Acting SPE) can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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